and Rubella Vaccines made determinations of causality only for rubella vaccine and the rubella vaccine component of multivalent vaccines, but not for measles-mumps-rubella vaccine (MMR). Thus, the Vaccine Safety Committee reviewed data regarding immunization with MMR as well as data on monovalent measles and mumps preparations. The committee has made separate determinations of causality for the measles and mumps vaccine components for the adverse events for which data were available, particularly if measles or mumps vaccine-strain virus was isolated from the patient. In circumstances in which a causality assessment specific to monovalent measles or mumps vaccine was not possible, this is stated in the conclusion regarding that specific adverse event.

In circumstances in which the committee determined that a component of a multivalent preparation was causally related to a specific adverse event, but there is no direct experience of such an adverse event being caused by the multivalent preparation, the committee states this, but judges that the combined preparation also is causally related to that adverse event.

Many case reports described an adverse event(s) in a patient who received more than one vaccine. A common combination, as a result of the immunization schedules recommended in the United States, is DPT, oral polio vaccine, and Hib vaccine. Assessment of causality in those reports was more difficult than if the patient had received only one vaccine or vaccine component, but the committee considered that the reports could be theoretically supportive of causality for the combination but not in themselves sufficient to allow a firm judgment regarding causality.

CAUSALITY AND WEIGHT OF EVIDENCE

As discussed in detail in Chapter 2, the committee considered four types of evidence: biologic plausibility; case reports, case series, and uncontrolled observational studies; controlled observational studies; and controlled clinical trials. The committee used qualitative and quantitative approaches to weigh each type of evidence. Table 1-1 contains a summary of the different types of evidence for every vaccine-adverse event relation studied. The committee believes that although it is plausible that there is a causal relation between any of the vaccine-adverse event associations under review, plausibility has been demonstrated only for certain ones of these. Therefore, information on the plausibility of a causal relation was classified in Table 1-1 as either theoretical only or as demonstrated. The other types of evidence were classified in Table 1-1 as nonexistent, indeterminate, or as weighing, on the whole, for or against a determination of a causal relation. The consideration of all four types of evidence as a whole led to a conclusion of the final weight of evidence regarding causality. Table 1-2 contains these conclusions.

detail below in the same order in which they will be considered within each of the vaccine- and adverse event-specific chapters.

Biologic Plausibility

All of the vaccine-adverse event associations assessed in this report have some biologic plausibility, at least on theoretical grounds. That is, a knowledgeable person could postulate a feasible mechanism by which the vaccine could cause the adverse event. Actual *demonstration* of biologic plausibility, however, was based on the known effects of the natural disease against which the vaccine is given and the results of animal experiments and in vitro studies. Only demonstrated biologic plausibility was considered by the committee in reaching its causality judgments.

Case Reports, Case Series, and Uncontrolled Observational Studies

The committee obtained reports of individual cases of adverse events following receipt of vaccine through the published medical literature as well as from passive, spontaneous surveillance systems established by the vaccine manufacturers, the U.S. Food and Drug Administration, and the Centers for Disease Control and Prevention. These include the Monitoring System for Adverse Events Following Immunization and the Spontaneous Reporting System, as well as the more recent Vaccine Adverse Event Reporting System (VAERS). Appendix B identifies the material from these systems obtained and reviewed by the committee. Chapter 10 includes a discussion of the limitations of passive surveillance systems such as these, as well as an analysis of the data contained within VAERS regarding reports of deaths following vaccination.

Uncontrolled observational studies are usually based on a cohort design, in which an identified group of vaccinees is followed for some period of time to detect the occurrence of one or more adverse events. These studies often incorporate more active surveillance than is the case in the passive, spontaneous reporting systems mentioned above, although a clear distinction from case series emanating from defined population bases is often difficult. Because no nonexposed control group is included in such studies, however, the rates of occurrence of the adverse events under consideration can usually be interpreted only descriptively, and the evidence derived therefrom is rarely helpful in either accepting or rejecting a causal relation. Also included under uncontrolled observational studies are reports of vaccine exposure in a representative group of individuals experiencing the adverse event. Such studies can also overlap with case series, although the authors of case series often attempt to make causal inferences (or hypotheses) concerning exposure to vaccines and/or other factors and, hence,

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